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# COVID-19 INFECTION-ASSOCIATED CHANGES IN LIVER FUNCTION TEST AND MATERNAL AND NEONATAL OUTCOMES IN INDIAN PREGNANT PATIENTS: PROSPECTIVE ANALYSIS

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## ABSTRACT

**Background:** The objective of the study was to observe the trend of changes in liver function and maternal and neonatal outcomes in COVID-19-positive pregnant women. **Methods:** The design of the study was a prospective observation study. The study was conducted at Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi. A total of 142 pregnant women with confirmed COVID-19 infection were recruited and studied prospectively between May 2020 and April 2021. The study population was divided into 2 groups symptomatic and asymptomatic COVID-19-positive pregnant patients. The trend of liver function was observed in the two study groups. Maternal outcomes in terms of mode of delivery and indication of cesarean section and adverse maternal and neonatal outcomes in terms of fetal weight and Apgar score. **Result:** The comparison of trends of liver function tests were compared in both study groups. Liver enzymes that is AST, ALT and ALP were increased in both groups, whereas else LDH was within the normal range. However adverse maternal outcome was observed in 12.7% of symptomatic group patients ($p<0.05$). There was no difference in observation in the mode of delivery, Apgar score and MSB (macerated still birth) in both study groups. However Low birth weight baby was observed at 32.9% in the symptomatic group as compared to 25.4% in the asymptomatic group. **Conclusion:** From the observation of our study, we recommend doing liver function tests (LFT) in all COVID-19-positive patients as it is associated with adverse maternal outcomes and follow the growth of the fetus in the antepartum period.

**KEYWORDS:** Covid-19, LFT, pregnancy, maternal, neonatal.

## INTRODUCTION

The global pandemic caused by the novel coronavirus, officially named severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), Coronavirus disease 2019 (COVID-19), originated in Wuhan, China, towards the end of 2019.[1] COVID-19 virus is a RNA virus. It exhibits the property of genetic mutation, as a result of which the virus undergoes continuous evolution in the genetic code during the replication of the genome.[2] SARS-CoV-2 has consistently mutated throughout the pandemic, resulting in variants that are different from the original SARS-CoV-2 virus. Various variants of clinical importance Omicron, alpha, beta, gamma, delta, epsilon, eta, iota, kappa, zeta, JN.1. The latest variant seen in India was JN.1. As of the current date, it has affected 702,930,005 individuals and tragically claimed the lives of 6,980,922 people, with daily increases in these numbers. As of now, the total census of COVID-19 cases stands at 4.50 billion, with the national recovery rate standing out to be 98.81%. COVID-19 virus primarily affects the respiratory system, but has the potential to impact various bodily systems, including the respiratory, intestinal, hepatic, and nervous systems.[2] According to various meta-analyses done on COVID-19 disease, the most common clinical presentation includes fever, cough, shortness of breath, myalgia, fatigue, headache and altered smell and taste sensation. However covid-19 disease can progress, severe outcomes such as acute respiratory distress syndrome (ARDS), multiorgan disease (MOD), and, in severe cases, fatality.[3-5] The biomarker of hepatocyte damage includes alanine aminotransferase(ALT), aspartate aminotransferase(AST), alkaline phosphatase(ALP) and lactate dehydrogenase(LDH) were commonly seen to be deranged in COVID-19 infected patient.[6,7] However, the pathomechanism of liver injury during infection is controversial and yet to be understood. SARS-CoV-2 virus enters the host cell through binding of its S protein to the ACE2 receptor on the surface of the host cells. The ACE2 receptor expression is higher in many organs such as the lungs, heart, and kidneys. Hepatocytes and bile duct epithelial

cells do express ACE2 receptors[5]. Studies show that cholangiocytes express more ACE2 receptors than hepatocytes. However the liver function abnormalities in COVID-19 infection appear multifactorial, that is it could be direct viral-induced liver damage or cytokine storm-induced or drug-induced hepatotoxicity.[6,7] The COVID-19 virus enters placental tissue and fetal circulation via the ACE2 receptors on placental cells. This is linked to various obstetric and fetal outcomes.[6,7]

## MATERIALS AND METHODS

A descriptive-analytical observational study was conducted in the Department of Obstetrics and Gynaecology, Maulana Azad Medical College, and Associated Lok Nayak Hospital, New Delhi, Over one year between, 1st May 2020 to 30th April. All antenatal women admitted with a COVID infection were recruited irrespective of gestation period. Patients already on anticoagulation therapy and diagnosed with cases of liver disease and exposure to hepatotoxic drugs over the past three months were excluded. Routine clinical history like age, parity, socioeconomic status, and any associated risk factors such as diabetes mellitus, hypothyroidism, hypertension, and previous liver dysfunction was obtained. Relevant findings of the general and systemic examination were recorded. Baseline investigations were sent (complete haemogram, kidney function tests, serum electrolytes, coagulation profile (PT, INR, aPTT, fibrinogen, D-dimer), and liver function tests along with all antenatal investigations. Repeat liver function tests were done on day 1, day 4, and the day before discharge (7 or 14 days). Trends of liver function tests were compared between symptomatic and asymptomatic groups. Adverse outcomes in the study included ICU admission and death. ICU admission criteria included study subjects who required mechanical ventilation or had a fraction of inspired oxygen (FiO2) of at least 60% or more, shock identified by the use of vasopressor therapy, and elevated lactate levels (>2 mmol/l) despite adequate fluid resuscitation or failure of other organs. The results were analyzed using the Chi-square and Fisher's exact tests.

## RESULTS

The mean age of the study subjects was 27.31±4.41 years (Table 1). Liver enzymes that is AST, ALT and ALP were increased in both groups, whereas else LDH were within the normal range. However adverse maternal outcome was observed in 12.7% of symptomatic group patients ($p<0.05$). 11 patients had adverse outcomes which included ICU admission or mortality. There were no adverse outcomes in the remaining 131 patients (table 2). There was no difference in observations in the mode of delivery, Apgar score and MSB in both study groups. However Low birth weight baby was observed at 32.9% in the symptomatic group as compared to 25.4% in the asymptomatic group (Fig 1).

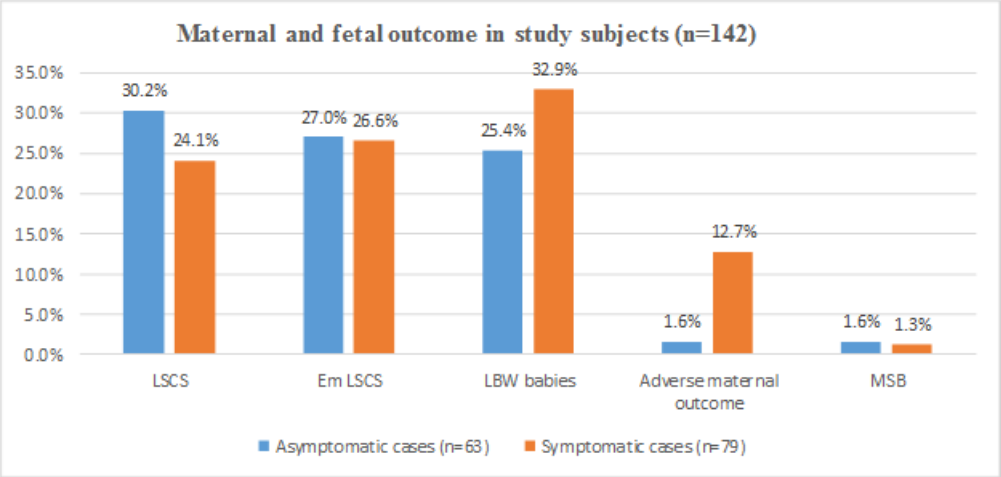


**Figure 1: Maternal and Fetal Outcomes in Study Subjects.**

**Table 1: Sociodemographic Profile of Study Subjects (n=142).**

| | No. | % |
|---|---|---|
| **Age group** | | |
| 18-25 years | 53 | 37.4 |
| 26-30 years | 61 | 42.9 |
| 31-35 years | 25 | 17.6 |
| >35 years | 3 | 2.1 |
| Mean age | 27.31±4.41 years | |
| **Socioeconomic status** | | |
| Upper middle | 30 | 21.1 |
| Middle | 57 | 40.1 |
| Lower middle | 55 | 38.7 |

| | | |
|---|---|---|
| **Parity** | | |
| Primi | 55 | 39.7 |
| Multi | 87 | 61.3 |
| **POG at admission** | | |
| 2nd trimester | 2 | 1.4 |
| 3rd trimester | 140 | 98.6 |
| **Comorbidity/risk factors** | | |
| Absent | 83 | 58.5 |
| Present | 59 | 41.5 |
| **Obstetric risk factors** | | |
| Absent | 56 | 39.4 |
| Present | 86 | 60.6 |

**Table 2: Liver Function Test Both Groups.**

| | Asymptomatic (n=63) | Symptomatic (n=79) | Overall (n=142) | p-value |
|---|---|---|---|---|
| **Platelet count** | 1.64±0.66 | 1.72±0.72 | 1.69±0.69 | 0.65 |
| **ALT** | | | | |
| **1st** | 49 (26-137) | 41 (23-92) | 44 (23-106.5) | 0.12 |
| **2nd** | 50 (23-117) | 50 (26-75) | 50 (25-92) | 0.55 |
| **3rd** | 56 (28-102) | 46 (29-90) | 56 (28.75-96.5) | 0.89 |
| **ALP** | | | | |
| **1st** | 286.0±136.24 | 254.71±112.36 | 268.59±124.05 | 0.26 |
| **2nd** | 229.68±90.19 | 243.96±109.43 | 237.63±101.25 | 0.41 |
| **3rd** | 263.38±126.59 | 241.22±111.88 | 251.05±118.72 | 0.39 |
| **AST** | | | | |
| **1st** | 56 (33-145) | 47 (28-99) | 51 (29.75-111.25) | 0.23 |
| **2nd** | 65 (39-128) | 53 (35-89) | 55.5 (37-108.25) | 0.20 |
| **3rd** | 68 (42-117 | 60.5 (37-104.25) | 62 (38.5-109.5) | 0.62 |
| **LDH** | | | | |
| **1st** | 345.06±89.24 | 367.47±233.85 | 337.53±184.18 | 0.37 |
| **2nd** | 327.95±103.12 | 327.30±143.24 | 327.59±126.59 | 0.76 |
| **3rd** | 347.44±109.34 | 367.71±122.47 | 358.72±116.86 | 0.23 |

**Table3: Indication of LSCS.**

| Indication of LSCS | No. | % |
|---|---|---|
| NPOL | 8 | 10.5 |
| Failed induction | 7 | 9.2 |
| MSL/Foetal distress | 13 | 17 |
| Previous LSCS | 28 | 36 |
| Multiple pregnancies | 4 | 5.2 |
| Malpresentation | 4 | 5.2 |
| Severe preeclampsia/eclampsia | 4 | 5.2 |
| Oligohydramnios | 3 | 3.9 |
| CPD | 3 | 3.9 |
| Maternal resuscitation | 3 | 3.9 |

## DISCUSSION

There are no changes in liver function during pregnancy. It has been observed through multiple studies, that COVID-19 infection causes hepatic injury. The majority of these studies were being conducted on the general population and limited data is available about the liver function changes and hepatic injury caused by covid virus in pregnant patients. Various conditions in pregnancy that are associated with liver dysfunction include preeclampsia, HEELP syndrome, viral hepatitis, and cholestasis of pregnancy. Pregnancy with deranged liver function parameters is considered a high-risk pregnancy. Hepatic injury during pregnancy is associated with the risk of antepartum haemorrhage, postpartum haemorrhage, DIC, and sudden IUD. A similar risk is imposed on the pregnant patient by the COVID-19 infection. Studies show that besides the risk imposed by liver dysfunction, COVID-19 infection during pregnancy can also cause fetal distress, meconium aspiration syndrome, low birth weight, and low Apgar at birth.

Hepatitis and hepatic failure in COVID-19-positive patients was not well studied. In our study, it was observed that both symptomatic and asymptomatic covid

positive showed mild to moderated derangement of liver function. Przekop D, et al found a 29.7% prevalence of liver injury in COVID-19 positive with severe disease, to those who did not have a liver injury.[6] Sekulovski M, et al comprehensive review of the database stated that the exact mechanism of liver injury in COVID-19-positive patients is under study.[7] Hepatic injury in COVID-19-positive pregnant women was a common finding, and managing liver injury during pregnancy is challenging and requires a multispecialty approach.

The clinical presentation of positive pregnant females is similar to nonpregnant. The majority of the symptomatic COVID + patients (n=79) in our study had mild symptoms like fever, cough, myalgia, and shortness of breath. 11 patients had adverse outcomes like severe pneumonia, ICU admission, and mortality. Khalil A, et al and Nayak A. H, et al showed 11% and 3% of patients to have adverse maternal outcomes like ICU admission and mortality respectively.

Krupa A, et al study 3% of the patients required ICU admission and 0 mortality was observed. Pregnancy is associated with a wide range of physiological, hormonal, and immunological changes, making it susceptible to acquiring infections. According to various studies available, pregnant women are susceptible to almost all infectious diseases affecting the upper respiratory tract.

Vertical transmission is not yet proved by any study. Therefore mode of delivery is currently based on obstetric factors and clinical urgency. Covid positive status is not an indication for caesarean section, however in critically ill patients for rapid maternal resuscitation caesarean section can be considered.[10] In our study 53% of COVID-19 delivered by C-section. Khalil, A., et al and Nayak A. H, et al, study 50% of patients in covid positive group delivery by caesarean section. Zaigham M, et al reported that 91% of COVID-19 of their patient were delivered by C-section.

Regarding the indication of C-sections majority of C-sections were due to definite obstetric indication, 17% were attributed to fetal distress and MSL, whereas only 3% were for maternal resuscitation in our study. Wang C-L, et al, majority of COVID-19 patients delivered by C-section.

The condition of neonates at birth born to COVID-19-positive patients was not much different than neonates born to COVID-negative patients. Apgar score at 1min and 5 min at birth in our study was observed to be 8-9. Krupa A, et al; Della Gatta A. N, et al; and Nayak A. H, et al showed normal Apgar scores at birth. In our study, Only 2 COVID-19 positive patients gave birth to MSB. Nayak A. H, et al, intrauterine fetal death was seen in 2.23% covid-19 positive as compared to 3.79% in covid negative patients. Della Gatta A. N, et al, One stillbirth and 1 neonatal death were observed in critically ill patients. Dashraath P, et al observed a 2% stillbirth rate and 2% neonatal death. Khalil A, et al perinatal deaths occurred in less than 1%.

In our study, low birth weight was observed in 25.4% of asymptomatic COVID-19-positive patients and 32.9 % in the symptomatic group. Nayak A. H, et al studied 29.71% of babies born to COVID-19-positive patients were low birth weight. Dashraath P, et al studied 9% of the newborns, that were low birth weight.

## CONCLUSION

The outcomes of COVID-19 infection in pregnant and neonates are not well studied. However, the studies were conducted and the present study suggests no major effect of COVID-19 infection on maternal and perinatal outcomes. Over the years, the healthcare system has been observed to be critical in managing COVID-19 infection in pregnancy. COVID-19 vaccination has added further immunity and protection. Viral pneumonia is the most common non-obstetric infectious disease in pregnancy. Any pregnant woman presenting with clinical features of LRTI, a strong suspicious of SARS should to kept and evaluated for the same. The present study highlighted the trend of liver function in COVID-19-positive pregnant patients. Since COVID-19 infection can lead to multi-organ dysfunction, pregnant patients with COVID-19 infection should be investigated and followed up for liver dysfunction. Since COVID-19 infection is associated with a lot of system changes, the usual obstetric complications preeclampsia, IHCP, and FGR can present with more severity. Therefore this patient needs vigilant care and follow-up. Also, long-term follow-up newborns is necessary to look for long-term adverse effects.

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